IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	: 10/678,145	Confirmation No. 1094
Applicant	: Babcock et al.	
Filed	: October 6, 2003	
Title	: COMPOSITIONS OF CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS AND HMG-COA REDUCTASE INHIBITORS	
TC/A.U.	: 1616	
Examiner	: Alstrum-Acevedo, James H.	
Docket No.	: 0003.0587/PC26122A	
Customer No.	: 00152	

APPEAL BRIEF

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April 28, 2010

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
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Real Party in Interest

The real party in interest by virtue of assignment is Bend Research, Inc., an Oregon corporation.

Related Appeals or Interferences

There are no related appeals or interferences.

Status of Claims

Claim 15 has been withdrawn. Claims 5, 6, and 9 have been cancelled. Claims 1-4, 7-8, 10-14, and 16-20 are pending and have been finally rejected in a Final Rejection dated July 30, 2009 (hereinafter referred to as the "Final Rejection"). A copy of the claims on appeal is set forth in Claims Appendix.

Status of Amendments

All amendments have been entered.

Summary of Claimed Subject Matter

All references in the following summary are to numbered paragraphs in US 2004/0132771, which is the published version of the application. Independent claim 1 is directed to a composition comprising: (a) a solid amorphous adsorbate comprising a cholesteryl ester transfer protein (CETP) inhibitor and a substrate [0012], wherein the substrate is selected from inorganic oxides, zeolites, clays, and activated carbons [1088]; wherein the CETP inhibitor is adsorbed onto the substrate; wherein the substrate has a surface area of at least 20 m^2/g; and wherein at least a major portion of the CETP inhibitor is amorphous [0012]; and (b) an HMG-CoA reductase inhibitor [0012].

Independent claim 20 is directed to a composition comprising: (a) a solid amorphous adsorbate comprising a CETP inhibitor, a substrate [0012], and a dissolution-enhancing agent [1137], wherein the substrate is selected from SiO_2, TiO_2, ZnO_2, ZnO, Al_2O_3, magnesium aluminum silicates, calcium silicates, $AlOH_2$, magnesium hydroxide, magnesium oxide, magnesium trisilicate, talc, and dibasic calcium phosphate [1088], and the dissolution-enhancing agent is selected from polyvinylpyrrolidone and poloxamers [1137]; wherein the CETP inhibitor is adsorbed onto the substrate, the substrate has a surface area of at least 20 m^2/g, and wherein at least a major portion of the CETP inhibitor is amorphous [0012]; and (b) an HMG-CoA reductase inhibitor [0012].

Ground of Rejection to be Reviewed on Appeal

The only issue on appeal is whether claims 1-4, 7-8, 10-14, and 16-20 are rendered obvious under 35 U.S.C. §103(a) by the combination of **Sikorski** WO 00/38722, **Gurtler** U.S. 5,773,021, **Mulligan** U.S. 5,128,142, **Rowe** US 2003/0099708, and **Jin** US 2004/0001888.

ARGUMENT

Prior Art Relied Upon

Sikorski discloses combinations of CETP inhibitors and HMG-CoA reductase inhibitors, but is silent as to (1) the need to increase the bioavailability of the CETP inhibitor, and (2) the use of a solid adsorbate to do so.

Gurtler discloses a "bioadhesive ophthalmic insert" for the prolonged release of medicinal substances into the eyes of humans and animals. Column 1, lines 10-48; Example 1. The ophthalmic insert comprises the medicinal substance incorporated into a matrix of composite polymers of either (i) 50 - 99.5 wt% of water-soluble biocompatible polymer and 0.5 – 5.0 wt% of a "bioadhesive" biocompatible polymer or (ii) two polymers of (i) in the same wt% with the balance to make up to 100 wt% a water-insoluble biocompatible polymer. A long list of the three types of polymers of the matrix is given in column 2; significantly, none of them may be characterized as inorganic oxides, zeolites, clays or activated carbons, as claimed in applicant's claim 1 or any of the 13 inorganic substances claimed in claim 20. There is no disclosure or suggestion that the Gurtler composition will improve the bioavailability of the medicinal substance delivered via the ophthalmic insert. Nor is there any mention of CETP inhibitors.

Mulligan discloses a controlled-release formulation comprising active and inactive ingredients adsorbed onto a cross-linked polymer. Abstract; Column 1, lines 50-55. An inactive substance such as polyvinylpyrrolidone (PVP) may also be adsorbed onto the substrate to modify the release of drug from the substrate. Column 1, lines 50-59; column 2, lines 48-52; column 3, lines 20-32. There is no disclosure or suggestion of the use of any CETP inhibitors or any of the substrates recited in claims 1 and 20.

Rowe discloses that the amorphous form of a drug leads to increased bioavailability of the drug. There is no disclosure or suggestion in **Rowe** to form a solid adsorbate, nor to use any of the substrates recited in claims 1 and 20. Most importantly, Rowe does not disclose or suggest the use of a solid adsorbate to increase a drug's bioavailability.

Jin discloses an oral composition of a drug dissolved in a lipid, which is then absorbed by a porous powder. Abstract. In Example 1, Jin describes the preparation of the composition by impregnation of an alumina/silica (Cab-O-Sil) mixture with the melted lipid Gelucire. Paragraphs [0056] – [0057].

Obviousness of Claims 1-4, 7-8, 10-14 and 16-20

The Examiner states at pages 5-6 of the Final Rejection that "Sikorski lacks the explicit teaching of amorphous drug, a composition in the form of an adsorbate, compositions comprising concentration-enhancing or dissolution-enhancing polymers, and the specific group of substrates recited in Applicants' claims." Since at least three of these four limitations are recited in all of the rejected claims, the Examiner concedes that Sikorski lacks at least three limitations of the rejected claims.

In an effort to overcome these glaring deficiencies of the primary reference Sikorski, the Examiner cites the four secondary references of Gurtler, Mulligan, Rowe and Jin, essentially arguing that, since the missing elements are supposedly found in the secondary references, it would have been obvious to combine such elements with Sikorski to obtain the claimed invention. (The Examiner's reliance on Rowe is unclear as to teaching any of the limitations missing from Sikorski, but if it is to support the proposition that the amorphous form of a drug increases its bioavailability, the point is conceded.)

The Examiner broadly concludes that it would have been obvious to modify the composition of Sikorski to absorb drug "onto or into a cross-linked polymer (e.g. a cellulose derivative) to obtain the benefits of a controlled-release formulation taught by (Gurtler) or onto other conventional solid supports, such as silica or alumina (Jin)." Final Rejection, page 6. This conclusion is flawed for at least three reasons: (1) applicants do not claim any substrate of a crosslinked polymer; (2) Gurtler does not

disclose a substrate or matrix of a cross-linked polymer; and (3) there is nothing in either Gurtler or Jin to the effect that Gurtler's matrix polymers are equivalent to Jin's inorganic porous particle substrates. As to reason (3), Gurtler teaches a bioadhesive ophthalmic insert, or a drug-releasing device to be placed in and left in a human or animal eye. Column 1, lines 5-20. To achieve such a device, a "bioadhesive biocompatible polymer" is required. Column 2, lines 5-7. Such a polymer is "a natural or synthetic polymer capable of stable interaction with a biological substrate, such as the mucosa of the conjunctional sac." Column 2, lines 34-37. Following the Examiner's logic, one of ordinary skill would substitute Jin's metal oxide powders of alumina or silica, both well known abrasives, for Gurtler's bioadhesive biocompatible polymers to be placed in a human eye. Why in the world would the skilled artisan place an abrasive in or near the eye? On its face this argument is not tenable. If this is the Examiner's argument, it is respectfully submitted to be a classic case of combining references such that the combination changes the principle of operation of the prior art device of Gurtler all the way to the point of rendering it unsatisfactory for its intended purpose, both of which are impermissible in an obviousness analysis. See *In re Ratti*, 123 USPQ 349 (CCPA 1959) and *In re Gordon*, 221 USPQ 1125 (Fed Cir 1984).

The Examiner's reliance on Mulligan is puzzling in two respects. First, it is undisputed that the Mulligan substrate is a cross-linked polymer; this would suggest the use of a cross-linked polymer as a substrate. But none of the rejected claims recite a substrate of a cross-linked polymer. Second, the Examiner states (erroneously), "Polyvinylpyrrolidone [PVP] is taught by Mulligan as being a suitable substrate onto or into which an API may be absorbed." Final Rejection, page 6. This would suggest the use of PVP as a substrate. But none of the rejected claims recite PVP as a substrate.

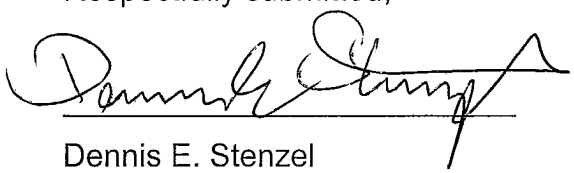
In contending that Jin teaches the claimed inorganic oxides, the Examiner has evidently deconstructed Jin's support, which is a lipid-loaded porous powder. See Jin at paragraphs [0056]-[0057] (Example 1), which describes the preparation of the support as impregnation of an alumina/silica mixture with the melted lipid Gelucire. But stripping away the lipid from Jin's porous powder particles would render Jin's invention inoperable as there would be no carrier or matrix for the solid solution of drug to be absorbed into the channels of the porous particles. See Jin FIG. 1. Again, as noted

above, if the proposed modification would render the prior art invention unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon,supra*.

Conclusion

For the reasons stated, the obviousness rejection is without merit and claims 1-4, 7-8, 10-14 and 16-20 should be allowed.

Respectfully submitted,



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Claims Appendix

1. A composition comprising:

(a) a solid amorphous adsorbate comprising a cholesteryl ester transfer protein inhibitor and a substrate, wherein said substrate is selected from the group consisting of inorganic oxides, zeolites, clays, and activated carbons, wherein said cholesteryl ester transfer protein inhibitor is adsorbed onto said substrate, and wherein said substrate has a surface area of at least 20 m^2/g, and wherein at least a major portion of said cholesteryl ester transfer protein inhibitor is amorphous; and

(b) an HMG-CoA reductase inhibitor.

2. The composition of claim 1 wherein said composition further comprises a concentration-enhancing polymer.

3. The composition of claim 2 wherein said solid amorphous adsorbate comprises said concentration-enhancing polymer.

4. The composition of claims 2 or 3 wherein said concentration-enhancing polymer is selected from the group consisting of neutral non-cellulosic polymers, ionizable non-cellulosic polymers, neutral cellulosic polymers, ionizable cellulosic polymers, acidic polymers, neutralized acidic polymers, and blends thereof.

7. The composition of any one of claims 1-3 wherein said HMG-CoA reductase inhibitor is selected from the group consisting of fluvastatin, lovastatin, pravastatin, atorvastatin, simvastatin, cerivastatin, rivastatin, mevastatin, velostatin, compactin, dalvastatin, fluindostatin, rosuvastatin, pitivastatin, dihydrocompactin and pharmaceutically acceptable forms thereof.

8. The composition of any one of claims 1-3 wherein said HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, the cyclized lactone form

of atorvastatin, a 2-hydroxy, 3-hydroxy or 4-hydroxy derivative of said compounds, and pharmaceutically acceptable forms thereof.

10. The composition of any one of claims 1-3 wherein said composition, following administration to an *in vivo* or *in vitro* aqueous environment of use, provides at least one of

(a) an improvement in the maximum concentration of said cholesteryl ester transfer protein inhibitor in said use environment of at least 1.25 fold relative to a control composition consisting essentially of said cholesteryl ester transfer protein inhibitor alone;

(b) an area under the concentration of said cholesteryl ester transfer protein inhibitor in said use environment versus time curve for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of a control composition consisting essentially of said cholesteryl ester transfer protein inhibitor alone;

(c) an improvement in the relative bioavailability of said cholesteryl ester transfer protein inhibitor of at least 1.25-fold relative to a control composition consisting essentially of said cholesteryl ester transfer protein inhibitor alone; and

(d) an improvement in the maximum concentration of said cholesteryl ester transfer protein inhibitor in the blood of at least 1.25 fold relative to a control composition consisting essentially of said cholesteryl ester transfer protein inhibitor alone.

11. The composition of any one of claims 1-3 wherein said solid amorphous adsorbate further comprises a dissolution-enhancing agent.

12. The composition of any one of claims 1-3 wherein said solid amorphous adsorbate has a dissolution rate constant of at least 0.005 min^{-1}.

13. The composition of any one of claims 1-3 wherein said substrate has a surface area of about 200 m^2/g or more.

14. A dosage form selected from the group consisting of a capsule, pill and tablet comprising the composition of any one of claims 1-13.

16. The composition of any one of claims 1-3 wherein said substrate is selected from the group consisting SiO_2, TiO_2, ZnO_2, ZnO, Al_2O_3, magnesium aluminum silicates, calcium silicates, $AlOH_2$, magnesium hydroxide, magnesium oxide, magnesium trisilicate, talc, dibasic calcium phosphate, zeolites, inorganic molecular sieves, kaolin (hydrated aluminum silicate), bentonite (hydrated aluminum silicate), hectorite, Na-montmorillonite, Al-montmorillonite, and Fe-montmorillonite.

17. The composition of claim 16 wherein said substrate is selected from the group consisting of SiO_2, TiO_2, ZnO_2, ZnO, Al_2O_3, magnesium aluminum silicates, calcium silicates, $AlOH_2$, magnesium hydroxide, magnesium oxide, magnesium trisilicate, talc, and dibasic calcium phosphate.

18. The composition of claim 17 wherein said substrate is SiO_2.

19. The composition of claim 11, wherein said dissolution-enhancing agent is selected from the group consisting of polyvinylpyrrolidone and poloxamers.

20. A composition comprising:

(a) a solid amorphous adsorbate, said solid amorphous adsorbate comprising a cholesteryl ester transfer protein inhibitor, a substrate, and a dissolution-enhancing agent, wherein said substrate is selected from the group consisting of SiO_2, TiO_2, ZnO_2, ZnO, Al_2O_3, magnesium aluminum silicates, calcium silicates, $AlOH_2$, magnesium hydroxide, magnesium oxide, magnesium trisilicate, talc, and dibasic calcium phosphate, and said dissolution-enhancing agent is selected from the group consisting of

polyvinylpyrrolidone and poloxamers; wherein said cholesteryl ester transfer protein inhibitor is adsorbed onto said substrate, and wherein said substrate has a surface area of at least 20 m^2/g, and wherein at least a major portion of said cholesteryl ester transfer protein inhibitor is amorphous; and

(b) an HMG-CoA reductase inhibitor.

Related Proceedings Index

Not applicable

Evidence Appendix

Not applicable